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CITATION:

NAKAMOTO, KOICHI. Quantitative Analysis of Postprandial Gastric Acid Secretion and Emptying by Measuring Gastric pH in Dogs. 日本外科宝函 1984, 53(1): 79-93

ISSUE DATE:

1984-01-01

URL:

<http://hdl.handle.net/2433/208752>

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Quantitative Analysis of Postprandial Gastric Acid Secretion and Emptying by Measuring Gastric pH in Dogs

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Received for Publication Oct. 7, 1983

Several techniques for the estimation of secretory and motor activity of the stomach have been employed in the diagnosis and measurement of peptic ulceration and other gastric pathophysiology. Gastric acid secretion tests have been developed: the dilution indicator technique was reported by Bandes⁵⁾ and by Hollander^{23,24)} in 1940, 24-hour-pH test by James & Pickering³²⁾ in 1949, cation exchange resin indicator compound by Segal⁵⁸⁾ in 1950, a serial test meal by Hunt²⁶⁾ in 1950, augmented histamine test by Callender⁹⁾ and Card⁸⁾ in 1960, by Baron⁴⁾ in 1962, by Kay³⁸⁾ in 1963, and by Laudano⁴²⁾ in 1965, augmented gastrin test by Abernethy¹⁾ in 1967, external γ scanning technique by Malagelada⁴⁵⁾ in 1977, a single scan technique by Taylor^{63,64)} in 1979, and dynamic gastric scanning by Keane³⁹⁾ in 1982.

Gastric emptying tests also have been devised: a serial test meal was reported by Hunt^{27,28)} in 1951, scintigraphic technique by Aeberhand, Hinder²²⁾ and Malagelada⁴⁵⁾ in 1977, by Read⁵⁵⁾ in 1980, by Dugas¹²⁾ in 1982, the dilution indicator technique by MacGregor in 1977, and the theoretical and empirical model of gastric emptying by Stubbs⁶²⁾ in 1977.

A more simplified, less harmful, and more comfortable method for the estimation of gastric acid secretion and gastric emptying under physiological conditions is clearly desirable.

A new method of continuous measuring of gastric pH in situ has been developed using an ion sensitive field effect transistor sensor. The theoretical analysis of gastric acid secretion after feeding of liquid meal is presented by measuring of gastric pH in situ.

Methods

Animal preparation

Three healthy mongrel dogs were prepared with a Heidenhain pouch with blood supply from the vasa brevia under general anesthesia with pentobarbital (Nembutal) 20 mg per kg. body

Key words: Gastric acidity, pH monitoring, pH sensor, Gastric secretion, Gastric evacuation.

索引語: 胃酸度, pH 測定, pH 電極, 胃液分泌, 食物通過.

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weight given intravenously. The pouch was drained by a stainless steel cannula. The pouch volume was approximately 20 cc. After 3 weeks recovery period, the dogs were surveyed for the estimation of the acidity of gastric secretion from the Heidenhain pouch. After more than 16 hours starvation, the dogs were fed test meal composing of 40 g minced meat (Vita One, Nippon Pet Food Co., LTD, Tokyo, Japan) per kg. body weight admixed with 20 ml of water per kg. body weight. The acidity of the secretion from the Heidenhain pouch was fairly constant (Fig. 1).

Other three healthy mongrel dogs of both sexes weighing 14 to 23 kg. body weight were investigated for the gastric motor and secretory activity. Under general anesthesia with pentobarbital sodium (0.4 ml of solution per kg. body weight) they were subjected to laparotomy. A stainless steel gastric cannula (6 mm in external diameter) was inserted into the gastric corp through the anterior wall near the greater omentum, and was fixed by a purse string suture. The cannula was passed through the greater omentum and its distal end was exteriorized through the left flank stub wound. A recovery period of at least three weeks was allowed before the dogs were used for experiment.

Measurement of pH

An ion sensitive field effect transistor sensor manufactured by Kuraray Co., LTD, Osaka, Japan was used. The flexible sensor is 30 cm in length and 2 mm in width. A transistor (diameter 0.5×1.5 mm) is attached at the end of the sensor (Fig. 2), which is connected to a pH meter (KR-500 pH/pCO₂ monitor, Kuraray, Co. LTD., Osaka, Japan) (fig. 3). The output of the pH meter was recorded by a pen recorder (KR-102 recorder Kuraray, Co. LTD., Osaka, Japan). The sensor was standardized at 37°C using buffer solutions of pH 4.01 and pH 6.86 (Kanto Chemical Co. LTD., Tokyo, Japan) before use. The response time for a shift between these pH values was below 0.5 seconds⁵⁰).

The sensor was inserted into the stomach through the gastric cannula and was fixed. After more than 16 hours fast, the dogs were fed a liquid meal composed of 40 g of minced meat

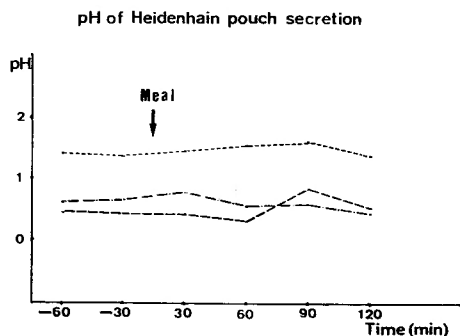


Fig. 1. The pH of the secretion from Heidenhain pouch.

The acidity of the secretion is fairly constant both before and after meal.

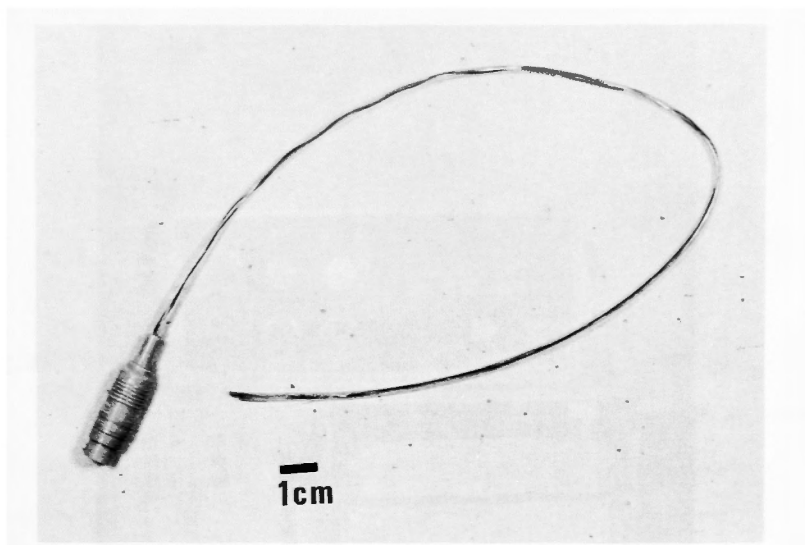


Fig. 2. The ion sensitive field effect transistor sensor.
A transistor sensor is attached at the end.

(Vita-one, Nippon Pet Food Co., LTD, Tokyo, Japan) per kg. body weight mixed with 20 ml of water per kg. body weight. The pH of the food was adjusted to pH 6.26. The pH was recorded at a speed of 1 cm per 15 minutes while measuring gastric pH changes.

Titration of food

Forty g of food of the same composition that were fed was stirred using a magnetic stirrer (Model PC-351, Iwaki glass, Tokyo, Japan) and titrated with HCl of different concentrations. The pH of food was adjusted to pH 6.26 before titration. Both the pH values and the volume of HCl admixed were recorded. Thus the titration tables and the titration curves could be obtained (Fig. 4). Using these titration tables, the ratios of the volume of HCl admixed to the total volume of solution at any pH values were easily calculated.

Measurement of gastric contents after feeding in vivo

The gastric content was aspirated through the gastric cannula and the weight was measured every 30 minutes. The content was reintroduced into the stomach through the cannula immediately after being weighed. The times used to aspirate and to reintroduce the gastric content were within 5 minutes. These procedures were continued until no gastric content was aspirated. The measurement of gastric content after feeding was performed five times in every dog. Thus the curves of the gastric content remaining in the stomach were obtained.

Theoretical Analysis

Figure 5 illustrates diagrammatically the in vitro model.

The conditions under which we did the analysis are:

- (1) The acidity of gastric secretion is constant during the postprandial period.



Fig. 3. KR. 500 pH/pCO₂ monitor (above) and KR-102 pen recorder (below).

- (2) The mean evacuation volume during the 15 minutes period from the stomach to the duodenum decreased linearly.
- (3) The process of mixing of the secreted gastric acid with gastric content is rapid.
- (4) Neither food nor gastric acid remains in the stomach when the pH value returns to the fasting pH value.
- (5) No water is absorbed into the gastric mucosa.
- (6) No hydrochloric acid is absorbed into the gastric mucosa.
- (7) The volume of duodenogastric reflux are negligible.

The mathematical equation

- (1) The mathematical expression of the average volume of content evacuating to the the duodenum during the period from 15(n-1) to 15n

$$B_{15n} = B_{15} \left(1 - \frac{15n-15}{T} \right)$$

T: the time when pH value returns to the fasting pH value after the zero time of the meal.
The zero time of the meal was the time at which the postprandial pH becomes most

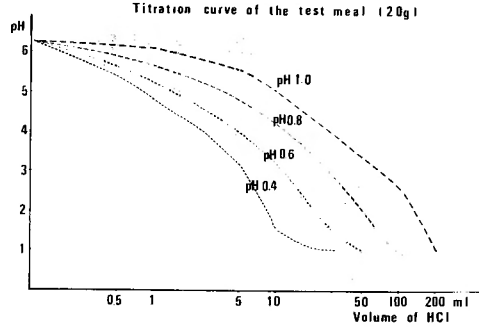


Fig. 4. The titration curves of the test meal (20 g) with HCl of pH 0.4, 0.6, 0.8 and 1.0 in vitro.
The ratios of the volume of HCl admixed to the test meal are easily calculated using this figure.

alkaline.

- (2) The mathematical expression of the volume of gastric acid remaining in the stomach at time $15n$ is expressed according to the formula.

$$V_{A15n} = V_{A15(n-1)} + 15A_{15n} - B_{15n} \int_0^{15} \left[k_{15(n-1)} + \frac{K_{15n} - K_{15(n-1)}}{15} t \right] dt$$

where

$15n$: the time from zero time of the meal

V_{A15n} : gastric acid remaining in the stomach at time $15n$

A_{15n} : the average volume of gastric secretion during the period between $15(n-1)$ and $15n$

V_{A0} : the volume of gastric acid remaining in the stomach at zero time

K_{15n} : the ratio of the volume of gastric acid remaining in the stomach to the total volume of gastric contents at time $15n$

- (3) The volume of food remaining in the stomach by the time $15n$ are given as:

$$V_{M15n} = V_{M15(n-1)} - B_{15n} \int_0^{15} \left[1 - \left(K_{15(n-1)} + \frac{K_{15n} - K_{15(n-1)}}{15} t \right) \right] dt$$

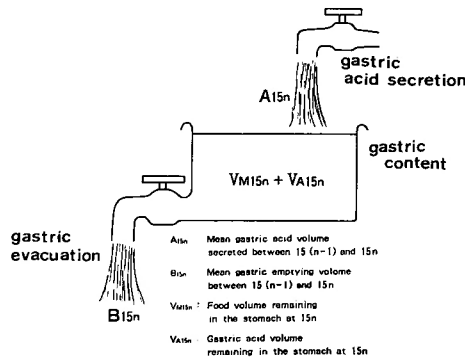


Fig. 5. The model of gastric secretion and gastric evacuation.

where

V_{M15n} : the volume of meal remaining in the stomach by the time $15n$

V_{M0} : the volume of food intake

The last equation was solved for B_{15} when V_{M15n} becomes 0.

Results

pH studies

The fasting gastric pH ranged from pH 0.4 to pH 1.0 and was fairly constant in these three dogs. There were rapid rises in pH following the meal and plateaus were maintained for about 2 to 13 15-min periods (Fig 6,7,8). Then the pH value decreased gradually and returned to the fasting pH level after 18 to 32 15-min periods. The gastric pH always fluctuated, so the pH value during any 15-min period was read as highest value during the period for theoretical analysis.

Theoretical analysis of gastric acid secretion and food remaining in the stomach

The volumes of gastric acid and food remaining in the stomach were calculated from the mathematical equations. Marked decrease in the volume of food as well as gastric acid in the stomach in a monoexponential pattern was seen in one dog (Fig. 6). In the other two dogs, there were plateaus in the volume of gastric contents during the 4 15-min periods, and the volume of gastric content gradually decreased in a complex exponential pattern (Fig. 7, 8)

Theoretical analysis of gastric evacuation and gastric acid secretion

The volume of gastric evacuation during the first 15-min period ranged from 105 ml per min and 150 ml per min. It was assumed that the average volumes of gastric evacuation during any 15-min period decreased linearly. Thus the volumes evacuated into the duodenum at any time were calculated using the above formulas.

The initial gastric acid volumes remaining in the stomach were calculated from the gastric pH when it became plateau after the meal. The calculated initial gastric acid volumes ranged from 37.8 ml to 78 ml.

The calculated gastric acid secreted after the meal was high during the 2 hours following the meal and then decreased remarkably.

Measurement of gastric content after the meal in vivo

The volume of gastric content decreased rapidly in a monoexponential pattern in one dog (Fig. 6). The emptying time in this dog was about 4 hours. The mean volume recovered from the gastric cannula when the pH value returned to the fasting levels was 29 ± 12 ml. In the other two dogs there were plateaus in the volume of gastric content during 1 hour after the meal and

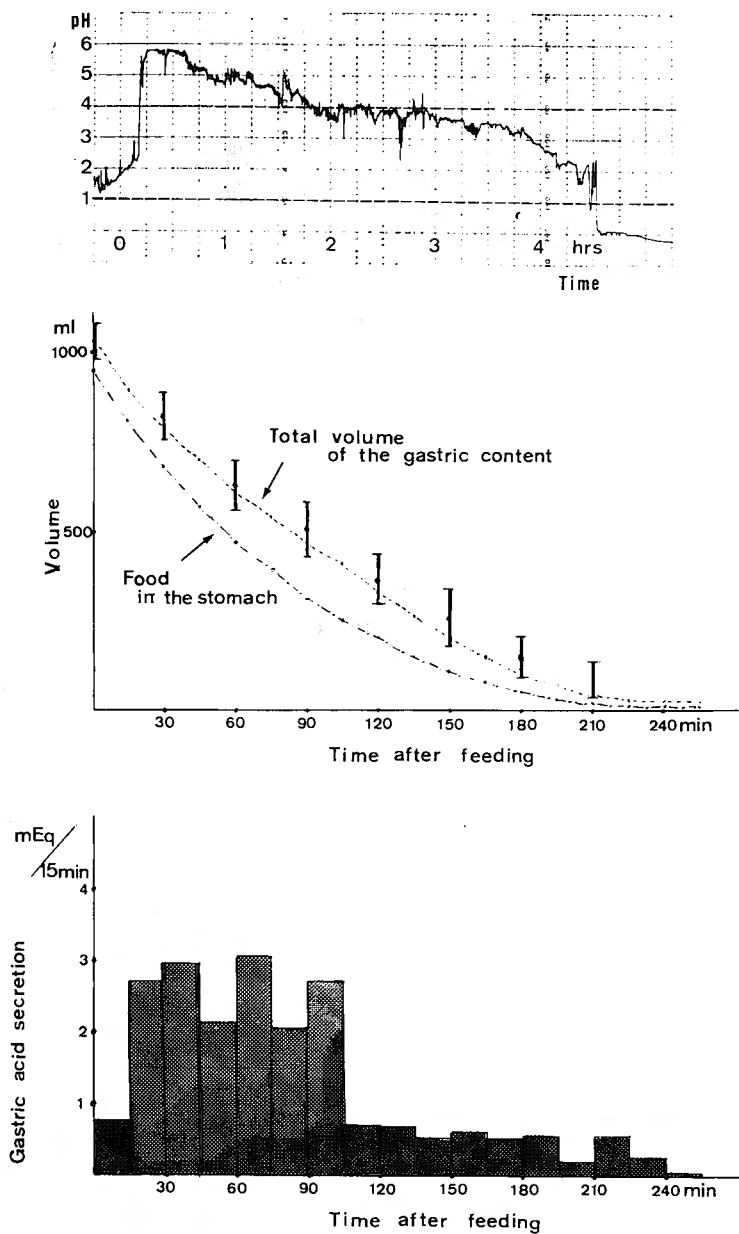


Fig. 6. The gastric pH after a meal (top).

The changes in the volume of the gastric content or food theoretically analysed (middle). The bars represent the mean and standard deviation of the volume of the gastric content observed in vivo (middle). It changed in a monoexponential pattern. The theoretically analysed gastric acid secretion during 15-min period after a meal (bottom).

the volume of content decreased gradually in a complex exponential pattern (Fig. 7, 8). The emptying time of the meal ranged from 8.0 hours to 8.5 hours. These data obtained in vivo

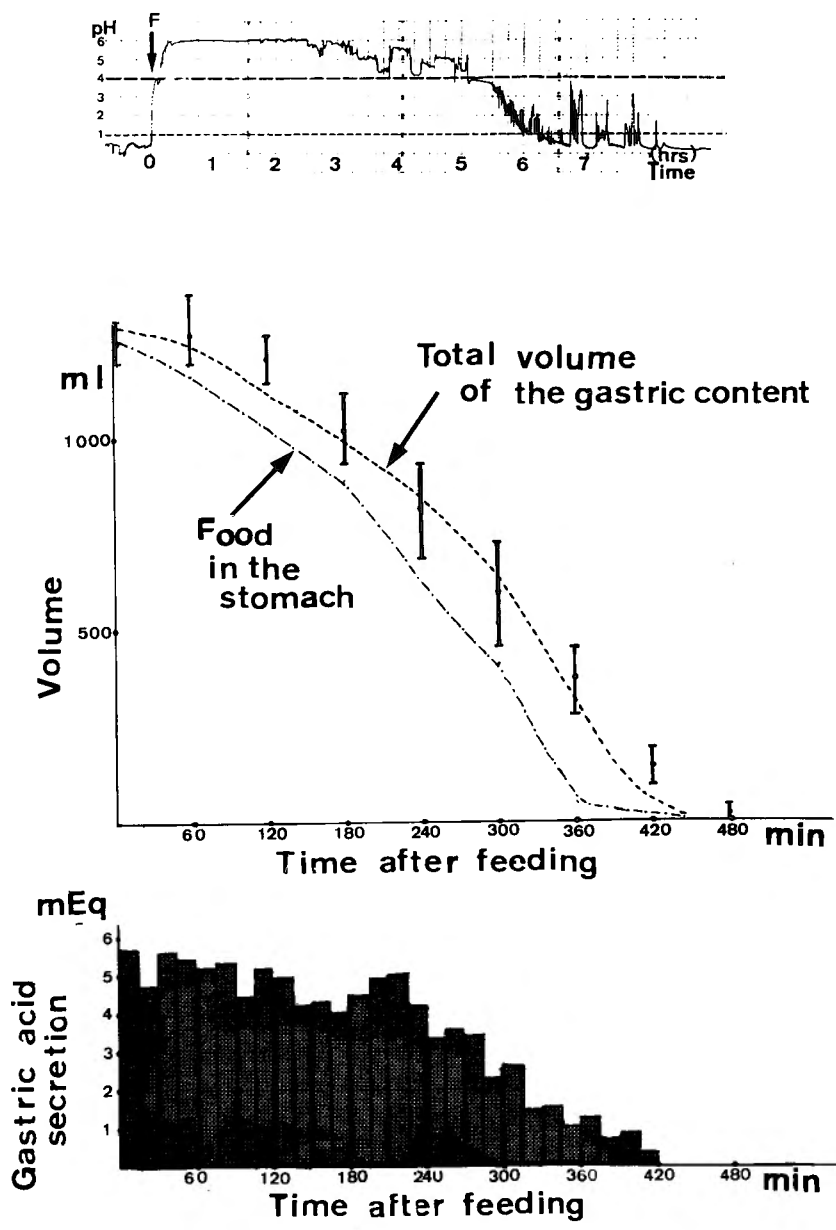


Fig. 7. The gastric pH after a meal (top). The volume of the gastric content changed in a complex exponential pattern (middle). The theoretically analysed gastric acid secretion was high in the early phase after a meal (bottom).

were compared with the data obtained by calculating from the formula. The theoretical curves obtained agreed well with the curves observed in vivo especially in the early course after the meal.

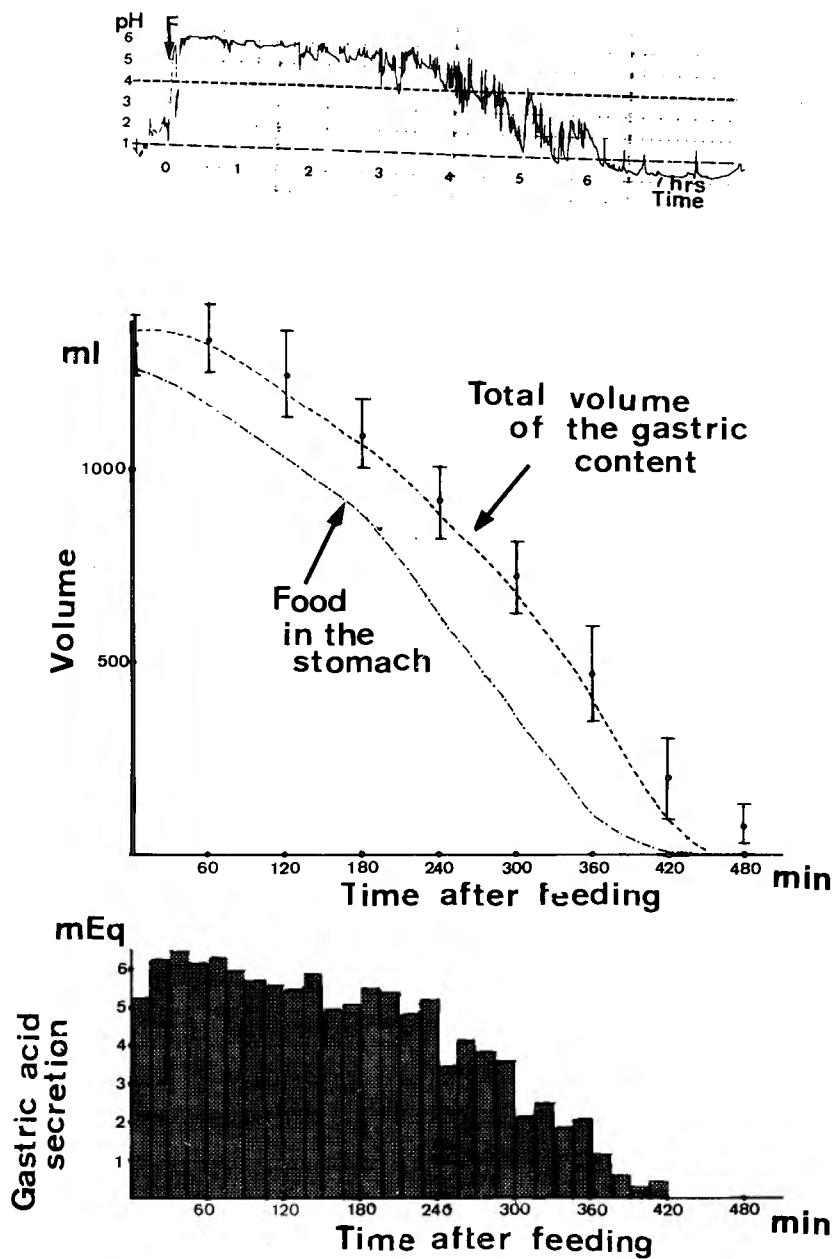


Fig. 8. The gastric pH value rapidly rose up to pH 6.0 and maintained a plateau for about 3 hours (top). The curve obtained by calculation were found to be extremely close to the mean value observed in vivo (middle). The theoretically analysed gastric acid secretion (bottom).

Discussion

First measurement of the upper gastrointestinal luminal pH in situ using a glass membrane electrode was credited to Flexner^{17,18)} in 1939. The telemetering system of monitoring the pH using an endoradiosonde equipped with a glass-electrode was developed by Mackay⁴⁴⁾ in 1957. These monitoring system of the pH in situ have been used to: elucidate the pathogenesis of peptic^{3,7,10,13,23,34,51} ulcers^{4,56,66)}, evaluate the effect of antacids^{15,57,61,65)} on gastric neutralization or the effect of cimetidine^{10,21,36,41,43,47,49)} or ranitidine⁶⁾ on the gastric secretion and to demonstrate gastroesophageal³³⁾ or duodenogastric reflux¹⁴⁾. However, no report has been made on the application of these pH monitoring system to evaluate gastric secretory or motor activity.

The gastric pH was almost always fairly constant during fasting and sometimes fluctuated between pH 6.0 and the basal pH value. These fluctuations during fasting seem to depend on the duodenogastric reflux. This study was started when the gastric pH became low and constant. After meal the gastric pH value rapidly rose up to about pH 6.0 because of buffering action of the meal. The pH remained at a plateau for a short time. The pH value of the plateau varied from day to day. This indicated that the basal gastric acid remaining in the stomach varied from day to day. This coincided with the findings of Baron⁴⁾. Then the pH decreased gradually to the fasting pH level. In the late stage of digestion, fluctuations in pH were noted.

The test meal composed of minced meat 40 g. per kg. body weight and water 20 g. per kg. body weight were stirred and homogenized into liquid. The advantages of a liquid test meal are as follows.

- (1) The mixing of the meal and gastric acid is so rapid that the monitored pH represents the pH of the gastric content. If a solid meal is given, it will take some time to make the meal homogeneous. When the content is not homogeneous, the recorded pH does not represent the pH of whole gastric content²⁰⁾.
- (2) Evacuation of a liquid meal into the duodenum is smooth and rapid. Some reports have been made on the evacuation of a liquid and a solid meal^{2,16,22,40)}. Hinder²²⁾ assessed the gastric emptying of a digested solid and a liquid meal simultaneously and concluded that the stomach empties liquid fast and retains solid for size reduction. Malagelada⁴⁵⁾ reported that the antepyloric region of the stomach is responsible for discriminating function which allows the liquid component of gastric bolus to pass through into the duodenum while returning most solid particles back into the stomach. Kelly⁴⁰⁾ stressed that the proximal stomach has a major role in gastric emptying of liquids and the distal stomach has a major role in gastric emptying of solid.
- (3) Clogging of liquid meal on the pH sensor rarely occurs because of low viscosity. If clogging of meal on the pH sensor occurs, the movement of gastric content easily remove the clogged food from the sensor.

Some other factors that affected the gastric emptying pattern were reported. Cooperman¹¹⁾ observed that the greater volume in the stomach, the more rapid the rate of emptying.

Hunt³¹⁾ found the greater the nutritive density of a meal, the less was the volume transferred to the duodenum in 30 min. He²⁹⁾ also demonstrated that the greater the concentration of

acid in the meal the greater was the volume of the meal recovered after a fixed interval. Hydrochloric acid and sulphuric acid were reportedly about three times as potent as potassium chloride in slowing gastric emptying³⁰⁾. Alcohol also stimulates gastric emptying³⁷⁾. The solid meal is evacuated slowly in a rectilinear pattern while the liquid meal is evacuated in a monoexponential pattern²⁷⁾ or in a complex exponential pattern¹⁹⁾. In this study to make the mathematical analysis easier, it was assumed that the liquid test meal was evacuated in a rectilinear pattern.

Water absorption was neglected in this analysis. It was reported that the mean absorption of water was 1.5%/hr. of the mean volume of water in the stomach.

Sonnenberg et al.^{48,60)} observed that duodenogastric reflux occurred both after meals and under fasting conditions and was independent of the rate of gastric emptying³⁷⁾. It was also reportedly independent of the presence of the pylorus. They found that the reflux rate was on the average 13 times smaller than emptying rate³⁶⁾. Ehrlein¹⁴⁾ noted that duodenogastric reflux occurred most often during the period of gastric emptying. Kalima³⁶⁾ observed frequencies of duodenogastric reflux were 10 to 13 percent. Thus the volume of the duodenogastric reflux was neglected.

Concerning the absorption of hydrochloric acid by a human stomach, Shay⁵⁹⁾ reported that approximately 0.5 to 1% were not absorbed. Hunt²⁵⁾ observed that the mean absorption of water was 1.5%/hr of the mean volume of water in the stomach. The absorption of hydrochloric acid was also neglected.

The theoretically analysed gastric acid secretion during the 15-min. period showed that the acid secretion is high during the early stage of digestion and decreases with time. These findings coincided well with the report of Cooperman.

The theoretical analysis of content in the stomach revealed that the volume in the stomach decreased in a monoexponential pattern in one dog, and in a complex exponential pattern in two dogs. There are reportedly two types of evacuation. Gordon¹⁹⁾ stressed that no gastric emptying curve is of a simple exponential type but rather of a complex exponential type where statistical analysis is difficult to perform. In our study the emptying pattern seemed to be dependent on the animal.

The measurement of gastric content in vivo was done five times in every dog. Hunt²⁷⁾ reported that there is no difference in the digestive activity between the swallowed meal and the meal introduced in the stomach through a tube. Thus it seems to be reasonable to assess the change in the gastric content by measuring the volume of aspirated contents and introduced it again into the stomach every 30-min. The curves of the volume remaining in the stomach in vivo were compared with those obtained by analysing the mathematical formulas. The curves obtained by calculation were found to be extremely close to the mean value observed in vivo.

In conclusion the mathematical analysis of gastric secretory and motor activity is fairly reasonable in evaluation of the gastric secretion and emptying after a meal.

Acknowledgement

The author wishes to express deep gratitude to Professor Dr. Yorinori Hikasa for his overall instruction. The author also thanks to Associate Professor Dr. Kisaku Satomura for his kind advice and fruitful discussion. A part

of this paper was reported in the 25th annual meeting of the Japanese Society of Gastroenterology held in Yamaguchi in October, 1983.

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和文抄録

胃内 pH 連続測定による胃液分泌動態の解析

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生理的な条件で、pouch を作成せず、食事刺激後の胃液の分泌動態を知りうることは、臨床的にも又、生理学的にも極めて意義のあるものと思われる。胃内の pH を連続的に測定しながら、試験食を与え、pH 値の変動より胃液の分泌動態を、数理的に解析することを試みた。

対象としては、体重15ないし 21 kg の雑種成犬 3 匹を使用した。pH 測定日の 3 週間前までに、ネブタール静脈麻酔下で、胃体部中央大彎側に胃棲を造設し、ステンレスカニューラを留置した。pH 測定は、クラレ製のイオン感応性電極 (ISFET センサー) をカニューラより胃内へ挿入した後、これをクラレ製 KR-500 pH/pCO₂ monitor に接続し、デジタル表示されるとともに、KR-102 レコーダーにて連続記録した。一方、試験食を pH 0.4, 0.6, 0.8, 1.0 の塩酸にて滴定し、滴定曲線を作成した。

他の 3 匹の雑種犬に Heidenhain pouch を作成し、食事前後の pouch からの分泌液の酸度を測定したが、酸度の変化は殆んど認めなかった。胃酸度の食後の経時的な変化がないと仮定するならば、滴定曲線より、pH 値がわかれば、その時点での胃液と食物との比は求められる。

解析する際に、以下の条件を設定した。

- 1) 食後に分泌される胃液の酸度は不変。
- 2) 十二指腸への排出は、一次元的に減少。
- 3) 食物と胃液との混合は急速。
- 4) pH 値が食前値に戻った時は胃内容物はない。
- 5) 胃からの水分吸収は無視。
- 6) 胃酸の胃壁からの吸収もなし。
- 7) 十二指腸胃逆流もなし。

以上の条件を満足する胃液分泌、十二指腸への排出等のモデルを考え、これを数式に表わして、これにて解析した。

結果：摂食直後の胃液量は、37.8 ml ないし 78 ml で、最初の15分間で十二指腸に排出された内容量は、105 ml ないし150 ml であった。胃内容物の量的変化は、一匹が指数函数的に、他の 2 匹が複指数函数的に変化した。胃液分泌は、摂食後の 2 時間が多かった。全食物排出時間は4.25時間から7.5時間であった。解析により得られた胃内容物の変化は、実測値に極めて近似していた。

結論：胃内 pH 連続測定による胃液分泌動態を解析したが、得られた値は実測値に極めて近似しており、食物摂取後の胃液分泌の動態は数理的に解析可能である。